Complete Summary

GUIDELINE TITLE

Use of preoperative chemotherapy with or without postoperative radiotherapy in technically resectable stage IIIA non-small cell lung cancer.

BIBLIOGRAPHIC SOURCE(S)

Cancer Care Ontario Practice Guideline Initiative (CCOPGI). Use of preoperative chemotherapy with or without postoperative radiotherapy in technically resectable stage IIIA non-small cell lung cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Apr. Various p. (Practice guideline; no. 7-4).

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Stage IIIA non-small cell lung cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Oncology
Radiation Oncology
Thoracic Surgery

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To make recommendations about the use of preoperative (neoadjuvant) cisplatin-based chemotherapy ± postoperative radiotherapy in technically resectable stage IIIA non-small cell lung cancer (NSCLC)

TARGET POPULATION

Adult patients with technically resectable stage IIIA non-small cell lung cancer (NSCLC)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Cisplatin-based chemotherapy
2. Surgery
3. Radiotherapy

MAJOR OUTCOMES CONSIDERED

- Survival
- Toxicity from chemotherapy
- Postoperative morbidity and mortality

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Practitioner feedback was obtained through a mailed survey of 148 practitioners in Ontario. The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations, and whether the draft recommendations should serve as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). A third reminder was sent at six weeks. The results of the survey were reviewed by the Lung Cancer Disease Site Group.

The practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Lung Cancer Disease Site Group and the Practice Guideline Coordinating Committee.

Update: April 2002

Because there was very little new evidence that emerged from updating activities and no modifications were made to the guideline recommendations, the updated document was not subject to an additional external review.

NUMBER OF SOURCE DOCUMENTS

September 1997 Guideline
4 randomized controlled trials

April 2002 Update
2 abstracts of randomized controlled trials

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

September 1997 Guideline

Survival data from two of the four randomized controlled trials (RCTs) were pooled to obtain a more precise estimate of the effect of preoperative chemotherapy and surgery with or without radiotherapy, versus surgery alone with or without radiotherapy. The third trial did not report survival data in a manner that allowed extraction of the data for this analysis. The results of the fourth trial were neither mature nor fully published and were therefore excluded from the pooled analysis. Odds ratios and 95% confidence intervals were calculated using a random effects model. Results are expressed such that an odds ratio greater than 1.0 favours the surgery alone arm and an odds ratio less than 1.0 favours the preoperative chemotherapy ± radiotherapy arm. The Meta-Analyst$^{0.988}$ program provided by Dr. J. Lau, Tufts New England Medical Centre, was used to perform this analysis.

April 2002 Update

A meta-analysis was not repeated with the two abstracts that emerged from updating activities since the available data were limited and there were indications of methodological problems with both. New evidence that is currently under review by the Lung Disease Site Group will be considered for data synthesis.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

September 1997 Guideline

The Lung Cancer Disease Site Group (DSG) deliberated extensively over the evidence on this topic. Although there is evidence from randomized controlled trials suggesting a benefit for patients treated with preoperative chemotherapy, there are concerns about the data reported in the two completed trials. The concerns include:

a. The small number of patients in the treatment arms of the trials. In one study, accrual was terminated early because of a statistically significant difference at the interim analysis; the alternative (i.e., not stopping the study) would have raised an ethical issue of continuing a trial despite an unanticipated huge difference that was highly significant, both statistically and clinically.
b. The inclusion of a heterogeneous group of stage III patients, including clinical stage IIIA patients in one study, 40% of whom proved to be stage IIIB upon pathological staging. An imbalance of stage III subsets between the arms of trials may contribute to, or be responsible for some of the observed differences in survival.
c. The prevalence of a known prognostic factor (mutated K-ras oncogenes) was different between the preoperative chemotherapy arm and the control arm of the Rosell study ($p=0.05$). This may account for some of the observed difference in survival between the two arms of this study.
d. The chemotherapy regimens administered in the trials are not comparable; there is a two-fold difference in the dose of cisplatin used in the two trials. However, given that the data are from randomized controlled trials (RCTs) and that both trials demonstrate a benefit for preoperative chemotherapy, the findings suggest that the intervention is effective at either dose of chemotherapy. The dose and schedule of the chemotherapy regimens would be problematic if the trial results were not consistent.
e. All subjects in the Rosell et al study received post-operative radiation treatment, as did a majority of subjects in the Roth et al study. It is impossible to assess the independent or interdependent contributions of the post-operative radiation to the main outcome of interest, which is survival. The improved result with preoperative chemotherapy may be due to the chemotherapy or to the combination of chemotherapy and radiation treatment. However, patients in both of the completed trials received radiation and thus, in the context of an RCT, this criticism is weak. The trials show that for patients who received postoperative radiation, preoperative chemotherapy works. The question then is whether this result can be generalized to patients who do not receive postoperative radiation.
f. Both trials were conducted in single institutions which may increase the risk of nongeneralizable results. While the potential for bias exists, this is the best available evidence at this time. The fact that there are two very positive completed RCTs with a third trial that appears to be positive lends credence to the findings; there is consistency in randomized trials for the benefit of

preoperative chemotherapy. The design and completion of a multicentre trial would enhance the generalizability of these findings.

g. The extremely large differences in survival were felt to be much greater than could reasonably be expected to occur. Although the magnitude of difference is large, the two trials described in this report independently found survival differences that were similar in magnitude. If, in fact, the findings are "too good to be true", it is more likely that the difference is smaller than observed rather than that there is no difference at all.
h. The inclusion of only a small number of T3N0 patients in these trials makes it impossible to comment on how this subset of stage IIIA non-small cell lung cancer (NSCLC) should be managed. The issue is how generalizable the findings are to the entire population of stage IIIA patients. Based on the data available, it is impossible to answer this question.

The preliminary results of the Cancer and Leukemia Group B (CALGB) trial do not confirm the survival benefit reported in the two completed trials. Further follow-up and analysis of the data is anticipated.

Members of the Lung Cancer DSG strongly support ongoing trials investigating management strategies for patients with stage IIIA disease. Such trials may investigate not only the role of preoperative chemotherapy, but also the role of preoperative radiotherapy or the role of combined preoperative chemotherapy plus preoperative radiotherapy in the treatment of patients with stage IIIA NSCLC.

April 2002 Update

The Lung Cancer DSG members agreed that although the new evidence was inconsistent with the data used to inform the original practice guideline report, its strength did not alter the conclusions or recommendations of the original document. Currently, the Lung Cancer DSG members are considering additional evidence that has emerged in 2000. This new information will be included in the guideline at the conclusion of their deliberations.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 148 practitioners in Ontario. The survey consisted of items evaluating the methods, results and

interpretive summary used to inform the draft recommendations, and whether the draft recommendations should serve as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). A third reminder was sent at six weeks. The results of the survey were reviewed by the Lung Cancer Disease Site Group.

The practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Lung Disease Site Group and the Practice Guideline Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Stage IIIA non-small cell lung cancer (NSCLC) has a number of different presentations including T3N0 (tumour with chest wall involvement without lymph node involvement) and N2 disease (mediastinal lymph node involvement on the same side of the mediastinum as the primary tumour). Although the surgical approach to patients with stage IIIA disease varies, it is generally accepted that T3N0 tumours should be managed by primary surgical resection. The role of surgery for patients who have histological evidence of N2 disease, however, is controversial. Many surgeons regard the presence of N2 disease as a contraindication to surgery.
- There is evidence from four small randomized controlled trials (12 to 32 patients per treatment arm) that for patients with technically resectable stage IIIA non-small cell lung cancer (NSCLC), the use of preoperative cisplatin-based chemotherapy and postoperative radiotherapy results in superior survival compared with surgery and postoperative radiotherapy. Whether the benefits of chemotherapy can be generalized to patients who do not receive postoperative radiotherapy cannot be determined from the existing trials.
- Although the interpretation of these trials is made difficult by their small size and the presence of retrospectively identified imbalances in prognostic factors, the available evidence led the Lung Cancer Disease Site Group to recommend that preoperative chemotherapy and postoperative radiotherapy be offered to patients with technically resectable histologically confirmed N2 disease for whom surgery is planned.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

September 1997 Guideline

Four relevant trials were identified for review. Two of the four trials are fully published and report final results, the third trial reports an interim analysis, and

the fourth trial reports preliminary results in an abstract published in the 1997 proceedings of the American Society of Clinical Oncology (ASCO). All four trials were designed to compare preoperative cisplatin-based chemotherapy followed by surgery against surgery alone in patients with technically resectable stage IIIA NSCLC. However, in three of the four trials, some patients received postoperative radiotherapy.

April 2002 Update

The new evidence includes two randomized controlled trials reported in abstract form. The new evidence is inconsistent with the data used to inform the original guideline report. However, the strength of the new evidence does not alter the conclusions of the original document. The features of the trials and results have been added to Table 1 in the full-text document. Additional evidence is currently under review by the Lung Cancer Disease Site Group.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

The data from two of the four trials reviewed were not combined because the data were not mature in one case and not extractable in the other. The two fully published, completed trials reported a survival benefit for patients treated with preoperative chemotherapy ± postoperative radiotherapy compared with patients who received no preoperative chemotherapy. One trial reported a median survival of 26 months for preoperative chemotherapy versus eight months for control ($p<0.001$). A second trial reported an estimated median survival of 64 months for preoperative chemotherapy plus surgery versus 11 months for control ($p<0.008$) and three-year survival of 56% versus 15% for the two treatment groups respectively. A pooled analysis of two-year survival data from the two completed randomized controlled trials yielded an odds ratio for death of 0.18 (95% CI 0.06 to 0.51) in favour of preoperative chemotherapy.

POTENTIAL HARMS

There was no difference in postoperative mortality in the trials reviewed. Toxicities associated with chemotherapy were limited primarily to neutropenic fever, nausea and vomiting.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Cancer Care Ontario Practice Guideline Initiative (CCOPGI). Use of preoperative chemotherapy with or without postoperative radiotherapy in technically resectable stage IIIA non-small cell lung cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Apr. Various p. (Practice guideline; no. 7-4).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1997 Sep 15 (updated online 2002 Apr)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Lung Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Provincial Lung Cancer Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Use of preoperative chemotherapy with or without postoperative radiotherapy in technically resectable stage IIIA non-small cell lung cancer. Summary. Toronto (ON): Cancer Care Ontario, 1997 Sep 15 (updated online 2002 Apr). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on January 5, 1999. The information was verified by the guideline developer as of February 22, 1999. This NGC summary was updated by ECRI on December 17, 2001. The updated information was reviewed by the guideline developer on January 10, 2002. This summary was updated on July 30, 2003. The updated information was verified by the guideline developer on September 2, 2003.

COPYRIGHT STATEMENT

Date Modified: 11/8/2004